REMARKS

This is in response to the Notice of Non-Compliant Amendment (37 CFR 1.121), dated May 8, 2006, requesting that claim 52 be resubmitted with underlining to indicate the added text.

Applicants acknowledge with appreciation the time and courtesies extended by the examiner toward Applicants' representative during the January 5, 2006 telephone interview conducted with Applicants' representative. The examiner's insights and comments have advanced the prosecution of the case. In particular, the outstanding rejections were discussed. All claims of record were also discussed and in particular claims 7 and 63. The allowable subject matter in claim 7 was highlighted. Discussions concerning the cited references was also discussed. Further discussion involved potential claim amendments in view of same and ways this matter can move forward.

Applicants address the examiner's remarks in the order presented in the Office Action (dated November 8, 2005). All claim amendments are made without prejudice and do not represent acquiescence in any ground of rejection.

AMENDMENTS TO THE SPECIFICATION

Sequence Listing

The sequence listing being filed concurrently herewith has been amended to correct several errors.

First, SEQ ID NO: 2, SEQ ID NO: 4 and SEQ ID NO: 6 were corrected in the July 12, 2004 Reply/Amendment and were renamed as SEQ ID NO:10, SEQ ID NO: 11 and SEQ ID NO: 12. Please see page 14 of the REMARKS section of the July 12, 2004 Reply/Amendment. Therefore, SEQ ID NO: 12 does not constitute new matter.

Second, SEQ ID NO: 13 was incomplete as filed with the July 12, 2004 Reply/Amendment. SEQ ID NO: 13 has now been amended as identified in FIG 6A-B. SEQ ID NO: 13 does not constitute new matter.

Next, SEQ ID NO: 14 was entered in error in the sequence listing filed with the amendment dated July 28, 2005. It was a duplicate of SEQ ID NO: 12. The sequence listing filed herewith has been amended to correct SEQ ID NO: 14 as identified in FIG 6A-B. Therefore, SEQ ID NO:14 does not constitute new matter.

STATUS OF THE CLAIMS

Claims 7, 52, 63, 65 and 67-74 are pending. Claim 6, 23 and 60, 61, and 69-72 were cancelled without prejudice. Claims 52, and 63-65 were amended. Support for the amendments to the claims can be found in the claims as filed. Support for the at least 95% identical" language, support can be found, for example, at page 16, line 29 through page 17, line 3. Claim 75 is new. Support the various Tir functions/activities can be found, for example, at page 9, line 18 through page 10, line 24. Support for claim 75 can be found in the claims as originally filed and throughout the specification. The specification was amended to correct SEQ ID NOs. and related sequence listing issues. No new matter is added by entry of this amendment.

The specification stands objected to under 35 U.S.C. § 132 because the examiner stated that previous amendments added new matter.

Claim 65 and those dependent therefrom stand rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claim 52 stands rejected under 35 U.S.C. § 112, first paragraph, as lacking written description (new matter).

Claims 69-72 stands rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement.

Claim 63 stands rejected under 35 U.S.C § 102(b) as being anticipated by Webster *et al.* (Mechanisms of Development 38: 25-32, 1992).

SPECIFICATION – NEW MATTER

The specification was objected to under 35 U.S.C. § 132 because the examiner alleged that amendments filed previously added new matter. More specifically, the examiner stated:

(a) The 'RDEC-1' polypeptide is identified in the amended Figure 9A-B description on page 7, lines 27-28 as 'SEQ ID NO: 14', whereas line 16 of page 49, as amended, refers to 'RDEC-1' 'polypeptide' to be 'SEQ ID NO: 12'. The raw Sequence Listing as originally filed did not contain 'SEQ ID NO: 12'. Both the recitation of 'SEQ ID NO: 12' now added on page 49 and its sequence composition now added to the raw Sequence Listing filed 08/01/05 constitute new matter.

(b) The recitation 'SEQ ID NO: 5 nucleotide' added at line 16 of page 49 of the specification via the amendment filed 07/12/04 is new matter. This part of the specification, as originally filed, did not describe any 'nucleotide' having a specific SEQ ID number of 'RDEC-1'.

(c) The raw Sequence Listing filed 08/01/05 includes the recitation and composition of 'SEQ ID NO: 13', which was absent in the Sequence Listing originally filed. The recitation of 'SEQ ID NO: 12' on page 49 and its sequence composition as disclosed in the raw Sequence Listing filed 08/01/05 both constitute new matter.

(ii) The specification lacks reference to, or antecedent basis for, 'SEQ ID NO: 2', 'SEQ ID NO: 4', 'SEQ ID NO: 6' and 'SEQ ID NO: 13', which sequences are included in the

raw Sequence Listings filed 11/10/98 and 08/01/05, but are not referred to in the specification.

(iii) The amendments made to line 16 of page 49 of the specification and the brief description for Figures 9A-B are confusing and/or inconsistent. At line 16 of page 49 of the specification, the 'RDEC-1' polypeptide is identified in the amended description for Figures 9A-B on page 7, lines 27-28 as 'SEQ ID NO: 14', whereas line 16 of page 49, as amended, refers to 'RDEC-1' 'polypeptide' to be 'SEQ ID NO: 12'.

As stated above, applicants filed a new Sequence Listing to correct several errors introduced by the July 12, 2004 amendment. In addition, applicants amended the specification to bring it in line with the new Sequence Listing. Applicants respectfully request withdrawal of the objection to the specification under 35 U.S.C. § 132 in view of the new Sequence Listing submitted herewith as well as in view of the amendments to the specification.

REJECTIONS UNDER 35 U.S.C. § 101

Claim 65 and those dependent therefrom was rejected under 35 U.S.C. § 101 because the examiner stated that the claimed invention is allegedly directed to non-statutory subject matter.

The examiner is of the opinion that claim 65 does not sufficiently distinguish over fusion proteins as they exist naturally for example on EPEC or EHEC bacteria, because the claim does not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. According to the examiner, in the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter (citing *Diamond v. Chakrabarty*, 1980, 447 U.S. 303, 206 USPQ 193. The

examiner suggested that claim 65 should be amended to indicate the hand of the inventor, *e.g.*, by insertion of --- an isolated Tir polypeptide --- as is supported in the instant specification.

Applicants have amended claim 65 for greater clarity and consistency of claim language. Applicants have amended the claims as suggested by the examiner as outlined in the November 8, 2005 Office action and again repeated during the telephone interview. Without acceding to the propriety of the rejection of pending claims under 35 U.S.C. §101, Applicants respectfully request reconsideration of the claim as amended.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (NEW MATTER)

Claim 52 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 52, as amended, includes the newly added limitations: polypeptide 'that comprises at least one of the amino acid sequences set forth in SEQ ID NO: 10 and SEQ ID NO: 11'. By this, a polypeptide comprising both of the amino acid sequences set forth in SEQ ID NO: 10 and SEQ ID NO: 11 is encompassed within the scope of the claim. However, the examiner is of the opinion that there appears to be no descriptive support in the instant specification as originally filed for the now claimed pharmaceutical composition comprising a single polypeptide that comprises both SEQ ID NO: 10 and SEQ ID NO: 11. Therefore, the examiner considered the limitations in the claims to be new matter.

Applicants have amended claim 65 for greater clarity and consistency of claim language. Applicants have amended this claim as suggested by the examiner as outlined in

the November 8, 2005 Office action and summarized above. Without acceding to the propriety of the rejection of pending claims under 35 U.S.C. §112, Applicants respectfully request reconsideration of the claim as amended.

Claim 69 and those dependent therefrom were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description.

According to the examiner, claim 69 as amended includes the newly added limitations: wherein the Tir polypeptide 'has at least one amino acid residue in SEQ ID NO: 11' substituted with a conservative amino acid and wherein the Tir polypeptide 'has at least one amino acid .... Inserted into SEQ ID NO:....wherein the Tir polypeptide retains at least one Tir-specific antibody'. The term 'at least' has no upper limit and therefor includes indefinite number. However, there appears to be no descriptive support in the instant specification as originally filed for a polypeptide comprising an amino acid sequence that is substantially identical to SEQ ID NO: 11, wherein any number of amino acids is substituted, deleted or inserted as recited currently. Therefore, the above-identified limitations in the claim are considered to be new matter.

Applicants cancelled claims 69-72 without prejudice solely to advance prosecution. Without acceding to the propriety of the rejection of pending claims under 35 U.S.C. §112, first paragraph, applicants respectfully request withdrawal of the rejection in view of the amendments to the claims.

Claims 70-72 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description.

New claim 70 depends from new claim 69. The isolated Tir polypeptide of claim 69 comprising an amino acid sequence that is substantially identical to SEQ ID NO: 11 wherein

the Tir polypeptide (i.e., Tir variant) has at least one amino acid residue in SEQ ID NO: 11 substituted with a conservative amino acid, or at least one amino acid deleted from or inserted into SEQ ID NO: 11, wherein the Tir polypeptide retains at least one Tir-specific activity. Dependent claims 70-72 are drawn to Tir variant polypeptides which retain at least the ability to bind to intimin, the ability to nucleate actin in a host cell, the ability to activate a host cell signal transduction pathway, the ability to specifically bind to a Tir-specific antibody, or the ability to induce an immune response in a host to an organism that produces a Tir polypeptide, such as, enteropathogenic E. coli or enterohemorrhagic E. coli. The examiner is of the opinion that such Tir polypeptides (*i.e.*, variants) having the specifically recited Tir-specific activity is not supported in the specification, as originally filed. Furthermore, recitations such as 'host cell signal transduction pathway' and nucleate actin 'in a host cell' appear to lack descriptive support in the specification, as originally filed.

As discussed above, applicants cancelled claims 69-72 without prejudice solely to advance prosecution. Without acceding to the propriety of the rejection of pending claims under 35 U.S.C. §112, first paragraph, applicants respectfully request withdrawal of the rejection in view of the amendments to the claims.

REJECTION(S) UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

Claims 69-72 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

Applicants cancelled claims 69-72 without prejudice and added new claim 75. Applicants submit that new claim 75 is directed to subject matter clearly described in the specification, which would convey to a person having ordinary skill in the art that Applicants had possession of the claimed invention at the time of filing. Applicants submit that the

specification describes nucleic acids that encode an Tir polypeptide having an amino acid sequence of SEQ ID NO: 11 (*see, e.g.*, Figure 9) and functional fragments. Therefore the complete structure of these species of Tir-encoding nucleic acids of the claimed invention are described in the specification. Moreover, it is well established that the "description of a genus of...sequences may be achieved by means of a recitation...of structural features common to the genus"(*Regents of University of California v Eli Lilly & Co.*, 43 U.S.P.Q.2d 1398, 1406, Fed Cir. 1998). Hence, the Tir nucleic acids described in the specification are representative of the genus of claimed nucleic acid sequences because each nucleic acid molecule encodes an Tir polypeptide with at least 95% amino acid sequence identity to a Tir polypeptide of SEQ ID NO: 11, and variants thereof.

Applicants submit that the amended claims are directed to subject matter clearly described in the specification, which would convey to a person having ordinary skill in the art that Applicants had possession of the claimed invention at the time of filing. Applicants submit that the specification describes nucleic acids that encode an Tir polypeptide having an amino acid sequence of SEQ ID NO: 11.

Applicants respectfully submit that the specification describes methods for identifying nucleic acid molecules that encode Tir polypeptides and fragments or variants thereof that have at least one Tir epitope and even Tir activity (*see, e.g.*, the specification at page 9, line 18 through page 10, line 24; see also the Examples). Therefore the various nucleic acid molecules that encode polypeptides having at least 95% identity EspA polypeptides and fragments thereof of SEQ ID NO: 11, or variants having conservative substitutions, and having at least one Tir epitope or activity could be easily identified by a person having ordinary skill in the art with, at most routine experimentation. Consequently, each of the

claimed polypeptides (*i.e.*, the genus of polypeptides), have both a structural identity and a specified biological activity, as provided by the invention. In addition, as set forth above and as was known in the art at the time of filing, methods were available to make nucleic acid molecule fragments and variants encoding polypeptides having at least 95% identity with Tir polypeptide of SEQ ID NO: 11. The specification also provides algorithms useful for determining percent identity or percent conservation between variant sequences (*see, e.g.*, at page 16, line 29 through page 17, line 6). Therefore, a person having ordinary skill in the art would conclude that Applicants were in possession of the necessary attributes possessed by nucleic acid molecules encoding polypeptides at least 95% identical to Tir polypeptides and fragments thereof of SEQ ID NO: 11, or variants having conservative amino acid substitutions, and having at least one Tir epitope.

Noteably, the Board decided that claims directed to a naturally occurring amino acid (or polynucleotide) sequence at least 95% identical to the disclosed amino acid (or polynucleotide) sequence were enabled and met the written description requirement (*see Ex parte Bandman*, No. 2004-2319, (BPAI 2005); attached as Exhibit A).

Regarding written description, the Board noted that "[t]he written description requirement . . . does not require a description of the complete structure of every species with a chemical genus." The Board also compared the circumstances of the instant case with those faced by the Federal Circuit in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002). In *Enzo Biochem*, the Federal Circuit determined that an "[a]dequate written description may be present for a genus of nucleic acids based on their hybridization properties, 'if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar.' " (citing

Enzo Biochem). In the instant case, the Board determined that the genus of molecules defined by the claims was similarly limited and reversed the examiner's written description rejection.

With regard to the enablement rejection, the Board disagreed with the Examiner's assertion that in order to satisfy this requirement, the specification must provide guidance regarding the specific amino acid residues that are tolerant to change without affecting malate dehydrogenase activity. Instead, the Board deemed persuasive appellants' argument that because the claims were limited to naturally occurring sequences, nature will have determined the amino acid residues that are tolerant to change (*i.e.*, naturally occurring variants will presumably retain malate dehydrogenase activity). In particular, in reversing the Examiner's enablement rejection, the Board determined that the examiner had not provided sufficient evidence that a naturally occurring polypeptide that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 or a polypeptide encoded by a naturally occurring polynucleotide sequence that is at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2 would not retain malate dehydrogenase activity.

Ex parte Bandman is directly on point in this case. As such, for the purposes of satisfying 35 U.S.C. §112, the disclosure of a natural sequence in and of itself is generally sufficient for disclosing a variance for that sequence, and the examiner is required to provide evidence that such disclosure is insufficient in order to maintain a *prima facie* case of failure to comply with 35 U.S.C. §112, first paragraph. *Ex parte Bandman*, No. 2004-2319, (BPAI January 2005) (Non-Precedential).

Applicants cancelled claims 69-72 without prejudice and added new claim 75 solely to advance prosecution. Without acceding to the propriety of the rejection of pending claims

under 35 U.S.C. §112, first paragraph, applicants respectfully request withdrawal of the rejection in view of the arguments and amendments to the claims as discussed above.

REJECTION(S) UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 69-72 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Applicants cancelled claims 69-72 without prejudice solely to advance prosecution. Without acceding to the propriety of the rejection of pending claims under 35 U.S.C. §112, second paragraph, Applicants respectfully request withdrawal of the rejection in view of the amendments to the claims.

REJECTION(S) UNDER 35 U.S.C. § 102

Claim 63 was rejected under 35 U.S.C § 102(b) as allegedly being anticipated by Webster *et al.*, 1992, Mechanisms of Development 38: 25-32.

Without commenting on the appropriateness of the rejection, in order to expedite prosecution, Applicants have amended claim 63. Accordingly, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 102(b) as anticipated by the Webster publication be withdrawn.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants submits that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested.

If the examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1396.

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